IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Goldenberg	
Serial No.: 10/002,211	
Filed: December 5, 2001	
Title: METHOD OF TREATING IMMUNE DISEASE USING B-CELL ANTIBODIES	**EFS-WEB**
Group Art Unit: 1644	
Examiner: Chun Dahle	
Attorney Docket No.: IMMU-0003US1	
Confirmation No.: 5605	

REPLY BRIEF

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Sir:

In reply to the Examiner's Answer dated February 18, 2011, applicant responds to various points raised by the Examiner. The numbering system used in the brief will be followed here for clarity, although it is noted that the examiner's numbering system now differs, because she has combined A and B under her heading a).

A. The rejection of claims 78-86, 93-108, 114 and 116 under 35 USC 112, first paragraph, as failing to comply with the written description requirement, based on the terminology defining the active ingredient as "a B-cell antibody or fragment thereof, which specifically binds to a B-cell."

The examiner has dismissed appellant's comments in conjunction with the Foon and Dörner declarations. The examiner notes that "the Foon declaration argues that the genus of the B-cell antibodies share the function of binding B-cell antigen and asserts that the reference Foon *et al.* teaches a list of 30 monoclonal antibodies (to B cell surface antigen) available commercially. Additionally, Foon asserts that one of skill in the art, upon reading the instant specification, would understand that appellant is in possession of a method of the claimed B-cell antibody to treat immune diseases." In fact, this was echoed by Dr. Dörner, who attested that:

> after reading the specification of the above-identified application, I would understand that the applicant was in possession of a method of using B-cell antibodies generally to treat immune diseases, and not just the LL2 B-cell antibody specifically. The skilled artisan would understand that applicant's contribution to the art was the teaching that B cells generally could be used to treat immune diseases. The skilled artisan would not need to know the structure of particular B-cell antibodies in order to be apprised of the full scope of applicant's invention.

The examiner counters that "none of the species of the antibodies in the references cited by the Foon declaration are disclosed in the instant specification, nor are they incorporated by reference in the specification as filed. More particularly, she states that:

> contrary to appellant's reliance on known antibodies, it is noted that "the hallmark of written description is disclosure…[T]he test requires an objective inquiry in the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed and actual "possession" or reduction to practice outside of the specification is not enough; and a description that merely renders the invention obvious does not satisfy the requirement. Emphasis in original.

Significantly, this "rebuttal" by the examiner refers to "the perspective of a person of ordinary skill in the art" and to "an invention understandable to the skilled artisan." Dr. Foon's declaration provides just the very perspective which is necessary according to the examiner, that of the "skilled artisan." When submitting Dr. Foon's declaration, appellant established his credentials in the field of B-cell antibodies. Indeed, during one of the interviews in this case, Examiner Gambel referred to Dr. Foon's seminal review on B-cell antibodies, noting that he had often cited it during examination of his cases.

The examiner's refusal to accept Dr. Foon's statements is not on a challenge to his credentials as a skilled artisan, but is instead a direct attack on Dr. Foon's well-reasoned statements that:

- a skilled artisan would understand that appellant's contribution to the art was the teaching that B-cell antibodies generally could be used to treat immune diseases
- a large number of B-cell antibodies had already been developed by 1992, and had been demonstrated to have a commonality of function vis-a-vis their use in cancer

treatment, correlated to an ability to affect disease progression as a result of their binding

- the binding function of B-cell antibodies is one that is testable
- the skilled artisan does not need to know the structure of particular B-cell antibodies in order to be apprised of and practice the invention.

By refusing to accept Dr. Foon's statements, the examiner is elevating her opinion and status as a "skilled artisan" over that of a skilled artisan whose credentials as such have been established in the present record. However, the examiner has not established why her own credentials in the field of B-cell antibodies are at least comparable to those of Dr. Foon. Based on the current record, it is submitted that Dr. Foon has been demonstrated to be a skilled artisan in the field of B cell antibodies, that his statements should be entitled to significant weight by the Patent Office, and that refusal by the examiner to accept Dr. Foon's statements is improper. The issue is what a skilled artisan takes from a reading of the specification as to the inventor's possession. The appropriate person to inform the decision of whether applicant was in possession of the claimed invention at the time of filing is a person of skill in the art, particularly one who was skilled in the art at the time of filing of the application. Dr. Foon's declaration therefore should be dispositive on this issue.

The examiner reiterates that "the specification provides no structural description of B-cell antibody or fully characterized antigen other than the one specifically exemplified LL2 antibody" and "there is no described or art-recognized correlation or relationship between the structure of the invention, the B-cell antibody and it's [sic: its] ablation of normal cell or treatment of immune diseases." However, the Foon declaration addressed these points, with Dr. Foon attesting that:

> The skilled artisan would understand that the contribution to the art was the teaching that B-cell antibodies generally could be used to treat immune diseases. These B-cell antibodies have a commonality of function, in that they all bind to B-cell surface antigens. In another context, that of B-cell cancers, this commonality of function has been found to correlate to an ability to affect disease progression as a result of that binding (I have discussed this in paragraph 7 above). This binding function is one that is testable, as I described in paragraph 3 above, and the skilled artisan would not need to know the structure of particular B-cell antibodies in order to be apprised of, and to practice, the full scope of this invention.

This conclusion is repeated in the concluding paragraph of a second Rule 1.132 declaration submitted by applicant, that of Dr. Dörner. The examiner's continued requirement that the structure of the antibodies be contained in the specification is clearly refuted by the position of two skilled artisans.

Finally, the examiner finds that the post-filing evidence submitted by appellant to show that certain B-cell antibodies are effective in treating autoimmune disease is not persuasive. It is noted that QAS Brumback stated at the interview that she would consider such evidence highly probative. Thus, the examiner maintains that her perspective in this matter is superior not only to Drs. Foon and Dörner, but also to QAS Brumback.

B. The rejection of claims 93, 97-100 and 106-108 under 35 USC 112, first paragraph, as failing to comply with the written description requirement, based on the terminology "chimeric or hybrid antibody which binds multiple epitopes or antigens."

No response to appellant's arguments in Section B of the brief is included in the Answer under examiner's section a) beginning on page 18 of the Answer.

C. The rejection of claims 102 and 105 under 35 USC 112, first paragraph, as failing to comply with the written description requirement based on the terminology "B-cell immune disease."

Once again, the examiner has maintained her position in the face of statements from Dr. Dörner, a skilled artisan whose credentials likewise have been established in the record. Dr. Dörner immediately recognized that the reference in the disclosure of "antibodies that target the spleen," is a reference to a targeting of immune cells that reside in the spleen. He explains that B-cell hematologic abnormalities are a consequence of immune diseases in which the immune system is positively regulated, and immune thrombocytopenic purpura (ITP) is an example of such an immune disease. He also immediately made the connection between the term "immune disease" and "B-cell immune disease." Accordingly, the specification clearly shows that applicant possessed methods of treating B-cell immune diseases, and the specification conveys that to the skilled artisan, as evidenced by Dr. Dörner's statements.

In this regard, both Dr. Foon and Dr. Dörner read the term "immune disease" in conjunction with the focus in the present application on B-cells, and on the example of ITP, a disease which results from loss of control of normal B-cells, to understand that the term "immune disease" means "autoimmune disease." Thus, Dr. Foon noted that:

> the term is used in conjunction with a discussion of the use of a B-cell antibody and also in conjunction with a disclosure of the ablation of normal spleen cells. The most common immune diseases then, and now, are autoimmune diseases. Accordingly, I understand the term "immune disease" in the application and the claims to mean autoimmune diseases.

Similarly, Dr. Dörner understood "the term "immune disease" in the context of the present disclosure as referring to classical autoimmune diseases." This is the broadest reasonable interpretation of "immune disease" that is ***consistent with the specification***. As such, the declarations are highly probative on the issue of support for, and the interpretation to be given to, the term in issue, and clearly show that extension of the term "immune disease" by the examiner to disorders such as the allergic response of Chang is not an interpretation of "immune disease" that is consistent with the disclosure in the present specification of B-cell involvement.

D. The rejection of claims 114 and 116 under 35 USC 112, first paragraph, as failing to comply with the written description requirement, based on the terminology "a marker associated with a B cell."

The specification describes that a "marker" is an entity to which an antibody or antibody fragment binds. Thus, page 15, lines 8-9 references that "the antibody is an antibody or antibody fragment which specifically binds a ***marker*** produced by or associated with said cell or tissue." The specification references "markers," as set forth in the Brief. Accordingly, "an antibody or antibody fragment specific to a marker associated with a B cell" was clearly disclosed in the parent specification and the present claims *in ipsis verbis* and is not a "departure" from the specification and claims as originally filed.

Furthermore, a skilled artisan can readily determine whether an antibody or antibody fragment is specific for a marker associated with a B cell. There exist cultured cell lines that express various B cell antigens. A skilled artisan readily can assess whether an antibody binds to the B cell antigen on these cell lines, and therefore there is a testable functional activity associated with the term "specific for a marker associated with a B cell." This was addressed in Dr. Foon's declaration, in which he stated that "[B-cell] binding function is one that is testable, as I described in paragraph 3 above."

E. The rejection of claims 78-86, 93-108, 114 and 116 under 35 USC 112, first paragraph, as failing to comply with the enablement requirement.

The examiner maintains that the term "B-cell antibody" reads on any antibody that binds expressed "on or in" a B-cell (Answer at page 30, third paragraph). On page 11 of the Answer she

notes that "the specification discloses that the use of **intracellular** antigen as preferable over cell surface antigen," citing page 11 of the specification. However, the cited portion clearly discloses such preference in the context of "organ associated and organ specific antigens," and not in the case of B-cell antigens, which a skilled artisan understands to be surface antigens (see Foon declaration repeated references to "surface molecules of leukocytes" and "antigens/epitopes on the surface molecules of leukocytes)."

The examiner argues that pharmaceutical therapies in the absence of *in vivo* clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, *i.e.* the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo* therapeutic use, *i.e.*, such as adverse side effects prohibitive to the use of such treatment. In the first instance, it is noted that many of the examiner's concerns, *e.g.*, proteolytic degradation, inability to cross the mucosa or absorption by fluids cells and tissues where the protein has no effect, are not particularly applicable in the context of an antibody administered parenterally by sterile injection to bind with B-cells, a large percentage of which are in the bloodstream.

Furthermore, the examiner's concerns are countered by the statements in Dr. Foon's declaration that B-cell antibodies were disclosed prior to 1992 for therapy of B-cell cancers, where they would experience these same alleged problems. Dr. Foon cited an article on which he was lead author reporting one study in which patients were treated with the BA-1, BA-2 and BA-3 monoclonal antibodies to B cells, and another in which patients were treated with anti-B1antibody.[1] These studies both showed that the binding of B-cell antibodies to cancerous B cells affects disease progression, and counter the examiner's concerns.

F. The rejection of claims 78, 81-86, 102-105, 114 and 116 under 35 USC 102(b) as being anticipated by Meyer *et al.* (US Patent 4,861,579).

In response to appellant's arguments regarding Meyer, the examiner replies that

> during patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification. The broadest reasonable interpretation of the claims must also be

[1] "Immunologic Classification of Leukemia and Lymphoma" (Foon and Todd, *Blood*, 68(1):1-31 (1987),

> consistent with the interpretation of that those skilled in the art would reach. See MPEP 2111.

MPEP 2111 cites the Federal Circuit's *en banc* decision in *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005), which expressly recognized that the USPTO employs the "broadest reasonable interpretation" standard.

The Board's attention is drawn particularly to the words "***as it would be interpreted by one of ordinary skill in the art***," which *Phillips* adopted from *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364[, 70 USPQ2d 1827] (Fed. Cir. 2004). The examiner asserts that "the claimed 'B-cell antibody which specifically binds to a B-cell' or 'antibody specific to a marker associated with a B cell', *when given broadest reasonable interpretation consistent with the specification*, would read on any antibody that would bind to antigens expressed on a B-cell surface as well as intracellular antigens" (emphasis added) It is noted that the examiner has omitted the language "*must also be consistent with the interpretation of that those skilled in the art would reach*" which is cited in MPEP 2111. When the scope of the claim terms is seen from the perspective of the skilled artisan, it is clear the examiner's interpretation is inconsistent with Dr. Foon's statements that B-cell antibodies "all bind to B-cell surface antigens."

Dr. Foon provides probative evidence on the issue of how terms 'B-cell antibody which specifically binds to a B-cell' or 'antibody specific to a marker associated with a B cell' in the specification would be interpreted by one skilled in the art so that they are ***consistent with the specification***. His statements support that the broadest reasonable interpretation of this term does not include "intracellular antigens."

In any event, Meyer relates to use of an anti-B cell antibody for suppressing the immune response generated upon administration of a therapeutic agent administered either as a naked or a conjugated antibody. Accordingly, there is no disclosure in Meyer that the anti-B-cell antibody is used to ablate normal cells to treat a disease, rather Meyer teaches how to combat the side effects arising from therapy using, for diagnostic or therapeutic purposes, an antibody (page 2, lines 38-42). The treatment modality may, according to Meyer also be used in connection with the use of therapeutic antibodies in the treatment of autoimmune diseases (page 3, lines 47-49).

In other words, according to Meyer the side effects arising from the treatment of autoimmune diseases using antibodies may be treated using an antibody against the B-lymphocytes. Thus, Meyer teaches that the treatment "modality" may be also used in connection

with the use **of therapeutic antibodies** in the treatment of autoimmune diseases, *e.g.*, the anti-T lymphocyte OKT-3 antibody. Meyer notes that this T-cell therapy

> is accompanied by a strong B-lymphocyte response to the mouse antibody, which, at least in part, compromises this approved clinically-useful procedure, C. F. Shield II et al., Nephron 46: suppl. 1, 48-51 (1987)]. Use of the modality of this invention in conjunction with OKT-3 antibody and the like would enhance the efficiency of this procedure

i.e., by suppressing the immune response." In other words, according to Meyer the side effects arising from the treatment of autoimmune diseases using antibodies may be treated by using an antibody against the B lymphocytes. It does not teach ablating normal cells, as in claim 78, or treating an immune disease, as in claim 104.

While appellant understands that other Patent Offices and other examiners may reach different conclusions on patentability, it is noted that Meyer was cited both in US 7,811,570 and EP 1 393 750, and that in both of these cases the examiners found appellant's arguments persuasive regarding the failure of Meyer to teach ablation of normal cells and/or treatment of an immune disease.

G. The rejection of claims 78, 79, 81, 93, 102-107, 114 and 116 under 35 USC 102(b) as being anticipated by Bussel *et al.* (*Blood* 1988 72;1:121-127) as evidenced by de Grandamont *et al.* (*Blood* 2003 101;8:3065-3073).

The examiner continues to cite Bussel *et al.* as teaching a method of treating immune thrombocytopenic purpura by administering intravenous immunoglobulins (IVIG). She then relies upon Grandamont as evidence that IVIG of Bussel includes B-cell antibodies. Now, in the Answer, she elaborates that the IVIG in Bussel inherently ablates normal cells, so that "it does not appear that the claim limitation of ablating normal cells results in a manipulative difference in the methods steps when compared to the prior art disclosure

There is ample evidence in Bussel both that (i) IVIG does not include a therapeutically effective amount of a B-cell antibody, and (ii) the administration of IVIG does not in fact ablate normal cells. Indeed, Bussel discloses that "Many reports have shown that intravenous administration of high dose gamma globulin (IVGG) in adults with ITP can cause a dramatic and substantial rise in the platelet count *presumably by temporarily interfering with mononuclear phagocyte system Fc receptor function*." Thus, Bussel teaches only that IVIG include components that affect Fc receptor function. The FcRn receptor is not present on immune cells. As previously

noted, Bussel's teaching that Fc-fragments have the same activity in patients as IVIG goes against an assertion of any possible antibody effect of the preparation. Thus, Bussel discloses that IVGG contains components which target Fc receptor, not B cells, and that it acts by interfering with Fc receptor function, not by ablating normal cells, as presently claimed.

The primary disclosure in Grandamont which is cited by the examiner as teaching that IVIG contains B cell antibodies is the following sentence:

> Intravenous immunoglobulins (IVIGs) are concentrated immunoglobulin G (IgG) solutions prepared from the pooled plasma of 3000 to 15000 healthy donors and contain antibodies reacting against a large repertoire of self and non-self antigens.

This sentence in Grandamont *et al.* (and the remainder of the article as well) fails to provide the evidence urged by the examiner that IVIG contains B-cell antibodies which ablate normal cells. To the contrary, as its title indicates, Grandamont teaches that intravenous immunoglobulins actually induce the *in vitro* **differentiation** of human B lymphocytes and the secretion of IgG. According to Grandamont, administration of IVIG "allows the **proliferation** of human B lymphocytes for up to one month as well as the differentiation into antibody-secreting cells" (first full sentence on page 3066). Proliferation of B cells, even if only initially, is the opposite effect desired to overcome autoantibodies produced by B cells in immune diseases. In the Discussion, Grandamont surmises that IVIG "can directly affect human B lymphocytes by reducing the proliferation while increasing the differentiation and IgG secretion. We have also shown that IVIGs were able to stimulate human B lymphocytes to secrete antibodies reactive with many antigens." Grandamont further reasons that "In the absence of cell death, reduction of proliferation might indicate that the cells have been driven to differentiate. We have done flow cytometry analyses to determine if differentiation was affected... Taken together, these results indicated that B lymphocytes in the presence of IVIGs were stimulated to differentiate into Ig-secreting cells."

Thus, far from providing "evidence" that IVIG contains "a B cell antibody or fragment thereof which specifically binds to a B-cell, in a pharmaceutically acceptable injection vehicle, thereby to ablate the normal cells," Grandamont provides evidence that components of IVIG act to cause B cell differentiation into cells which secrete IgG. Thus Grandamont cannot be relied upon as evidence that the IVIG treatment of ITP in Bussel inherently contains any component, and more particularly a B cell antibody or fragment thereof, which acts in **ablation** of normal cells. Instead it teaches the presence of components which cause B cells to proliferate initially (the antithesis of immune disease therapy) and then differentiate into cells which create IgG.

H. The rejection of claims 78, 80, 93, 95-101, 107 and 108 under 35 USC 103(a) as being unpatentable over Meyer *et al.* (US Patent 4,861,579) in view of Sivam *et al.* (US Patent 5,116,944).

The examiner states that "given the teachings of Meyer *et al.* regarding method of treating an immune disease using anti-B cell antibody" and Sivam's teaching of Fv, single chain antibody, Fab, Fab', F(ab')2, chimeric antibody, and antibody that is conjugated to cytokine, that the claims would have been obvious. However, Meyer does not teach treating an immune disease using anti-B cell antibody, as discussed above.

I. The rejection of claims 78 and 94 under 35 USC 103(a) as being unpatentable over Meyer *et al.* (US Patent 4,861,579) in view of Fishwild *et al.* (*Nature Biotech.* 1996, 14:845-851).

The examiner combines Meyer's teaching with Fishwild's teaching of methods of making human monoclonal antibody and its use in therapy, that the claims would have been obvious. However, Meyer does not teach treating an immune disease using anti-B cell antibody, as discussed above.

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For these reasons, and those in appellant's brief on appeal, the Board is requested to reverse the decision of the examiner and pass the present case to issuance.

Respectfully submitted,

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APRIL 18, 2011
DATE

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